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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/635,924	08/05/2003	Kim Sze Tan	GJE04.FD1	1060

23557 7590 03/27/2007

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/635,924	TAN, KIM SZE	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/108,728.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/26/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 9 and 15 have been amended.

2. Claims 1-16 are pending and under consideration.

3. This Office Action contains New Grounds of Rejections.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 26 December 2006 has been fully considered by the examiner. A signed copy of the IDS submitted on 26 December 2006 is included with the instant Office Action.

All Objections/Rejections in the previous Office Action mailed 6/27/2006 are withdrawn in view of applicants' arguments, amendments to the claims and specification and in view of the submitted Board of Patent Appeals and Interferences decision from parent application USSN 08/425,682.

New Grounds of Objections/Rejections

Specification

5. The specification is objected to in the disclosure "It is clear that more hybridoma cell lines resulted from the SPF1 cross (total 634) than NS2 (total 634)." at pg. 8, lines 29-31 with reference to Table 1. Table 1 discloses the number of hybridomas for the SPF1 fusion and the NS2 fusion under different culture conditions, however the total number of hybridoma cell lines for the NS2 fusion is 226, not 634 as disclosed on pg. 8 of the specification. Applicants' cooperation is again requested in reviewing the entire disclose for additional errors that require correction.

Appropriate corrections and/or clarification is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for humanized and chimeric sheep monoclonal 17C6 antibodies or antigen-binding fragments thereof comprising the hypervariable regions (CDRs) of sheep monoclonal antibody 17C6, wherein the humanized and chimeric 17C6 antibodies have an antigen binding affinity of at least about 10^{11} l/mol, or at least about 10^{12} l/mol, or at least about 5 x 10^{12} l/mol, or at least about 10^{13} l/mol, or is less than about 10^{14} l/mol, wherein the humanized and chimeric antibodies retain the T3 antigen specificity of parental sheep monoclonal antibody 17C6, does not reasonably provide enablement for humanized and chimeric antibodies or antigen-binding fragments thereof comprising the hypervariable regions (CDRs) of high affinity non-rodent, non-human monoclonal antibody, or ovine antibody, wherein the humanized and chimeric antibodies have an antigen binding affinity of at least about 10^{11} l/mol, or at least about 10^{12} l/mol, or at least about 5 x 10^{12} l/mol, or at least about 10^{13} l/mol, or is less than about 10^{14} l/mol, wherein the humanized and chimeric antibodies do not retain the antigen specificity of the parental high affinity non-rodent, non-human monoclonal antibody, or ovine antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988).

> Wands states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is engineered or humanized and chimeric antibodies where the relative level of skill of those in the art is deemed to be high.

The claims are broadly drawn to humanized and chimeric antibodies or antigen-binding fragments thereof comprising the hypervariable regions (CDRs) of high affinity non-rodent, non-human monoclonal antibody, or ovine antibody, wherein the humanized and chimeric antibodies have an antigen binding affinity of at least about 10^{11} l/mol, or at least about 10^{12} l/mol, or at least about 5 x 10^{12} l/mol, or at least about 10^{13} l/mol, or is less than about 10^{14} l/mol. Thus, the claims broadly encompass a genus of high affinity non-rodent, non-human monoclonal antibodies, or ovine antibodies having affinities of at least about 10^{11} l/mol, wherein the humanized and chimeric antibodies do not retain the antigen specificity of the parental non-rodent, non-human, or ovine antibody.

The specification teaches the production of an ovine monoclonal antibody produced by fusion of sheep lymphocytes obtained after repeated immunization with T3-BSA conjugates *over a period of 15 years* in order to obtain polyclonal antiserum to T3 wherein the sheep lymphocytes were fused to a sheep heteromyeloma fusion partner (SPF1) or fused to NS1 myeloma cells. Two months post fusion, 57 cell lines were still weakly positive; one line resulting form the SFP1 x sheep spleen cross resulted in cell line 17C6, which was considerably stronger than the others and chosen for further study (see example 1, pp. 6-9). The specification teaches that the 17C6 cell line initially grew very slowly, but the growth rate increased such that the line divided at rates comparable with conventional murine and human lines (see pg. 9). The specification also teaches that the association constant for the sheep monoclonal antibody 17C6 was 2.6 x 10^{13} l/mol (see pg. 9). The specification does not teach any other high affinity non-rodent, non-human monoclonal antibody, or ovine antibody other than sheep monoclonal antibody 17C6 having an affinity of at least about 10^{11} l/mol. There are no working examples of humanized and chimeric high affinity non-rodent, non-human monoclonal antibodies, or ovine antibodies having an affinity of at least

about 10^{11} l/mol. Thus, the scope of the claims is extremely broad relative to scope of the disclosure. The scope of the claims must bear a reasonable correlation with the scope of enablement. See *In re Fisher*, 166 USPQ 19 24 (CCPA 1970).

The state of the prior art recognizes the advantages of preparing humanized and chimeric antibodies and suggests that non-rodent antibodies, such as ovine antibodies may have a higher affinity than murine antibodies, e.g., see Groves et al [a] at pg. 221, col. 2 (Journal of Endocrinology, 126:217-222, 1990, IDS reference R8 filed 5/3/04) and Queen et al [a] (US Patent 5,530,101, cited on PTO-892 mailed 6/27/2006) and Morrison S. L. (Science, 229:1202-1207, 1985, IDS reference R22 filed 4/30/04). While Groves et al [b] (Veterinary Immunology and Immunotechnology, 23:1-14, 1989, IDS reference R16, filed 4/30/04) describes an ovine monoclonal antibody to testosterone having an affinity K_D of 7.63×10^{-12} mol/l, the non-rodent antibodies such as the human or primate monoclonal antibodies to digoxin described by described by Ehrlich P. H. (Clinical Chemistry, 34(9):1681-1688, 1983, IDS reference R17, filed 4/30/04) have an affinity of 3×10^{10} l/mol, while the ovine monoclonal antibodies to digoxin described by Rainey P. M. (American Journal of Clinical Pathology, 92(6):779-786, 1989, IDS reference R21 filed 5/3/04) have dissociation constants centered around 10^{-9}-10^{-10} mol/l. Ehrlich, page 1683, col.2; Rainey, page 783, col.1. Buchegger et al (Journal of the National Cancer Institute, 79:337-342, 1987) teach two swine anti-CEA monoclonal antibodies having affinity constants of 1.2×10^9 and 1.2×10^{10} liter/mol. The art reasonably appears to indicate that non-rodent antibody affinity is dependent upon various factors, such as the nature of the antigen to which the antibody is raised and the structure of the variable regions of the antibody. For example, see pg. 10033, col. 1 of Queen et al [b] (Proc. Natl. Acad. Sci. USA, 86:10029-10033, December 1989, IDS reference R12 filed 5/3/04). As argued by applicant and stated in the Board decision from the parent of the instant application submitted by applicant "The cited references, in our view, indicate a level of unpredictability in the art having particular bearing on the expectation of success of obtaining a non-rodent antibody with an affinity of at least about 10^{11} l/mol, as claimed." (see pg. 7 of the board decision submitted 12/26/06). Further, the prior art establishes that the claimed technology was not well developed at

the time of filing. It is unlikely that one of skill in the art could predictably extrapolate the teachings in the specification to produce the genus of humanized and chimeric non-rodent, non-human monoclonal antibodies, or ovine antibodies having an affinity of at least about 10^{11} l/mol with any reasonable expectation of success in view that the disclosed method of immunising sheep over a period of 15 years with a T3-BSA conjugate produced only 1 out of 643 hybridoma cell lines or 0.15% of the lines resulting from the SPF1 x spleen cross that considerably stronger than the other 57 weakly positive hybridoma lines. There is insufficient evidence or nexus between the disclosed properties and characteristics of sheep monoclonal antibody 17C6 and the claimed genus of non-rodent, non-human monoclonal antibody, or ovine antibody having an affinity of at least about 10^{11} l/mol. Applicant has not provided sufficient data or authority to show that the disclosed results are reasonably predictive within the scope of the claimed generic invention, based on experiment and/or scientific theory or as established in the art at the time of filing. The specification does not enable the genus because where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one particular species, what other species will work (e.g., see also Board decision submitted 12/26/06). See MPEP 2164.03. One of skill in the art would neither expect nor predict the appropriate functioning of the humanized and chimeric non-rodent, non-human monoclonal antibody, or ovine antibody as broadly as is claimed.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Groves et al, Ehrlich P. H., Rainey P. M., Buchegger et al and Queen et al, the lack of guidance and direction provided by applicant, and the absence of working

examples, undue experimentation would be required to practice the claimed genus of humanized and chimeric non-rodent, non-human monoclonal antibody, or ovine antibody having an affinity of at least about 10^{11} l/mol with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed high affinity humanized and chimeric antibodies and absent working examples providing evidence which is reasonably predictive that the claimed humanized and chimeric antibodies retain the antigen binding specificity of the parental non-rodent, non-human monoclonal antibody, or ovine antibody, and have an affinity of at least about 10^{11} l/mol, commensurate in scope with the claimed invention.

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Blanchard
Patent Examiner
Art Unit 1643

DB
March 21, 2007